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Mumps increase in Flanders, Belgium, 2012–2013: Results from temporary mandatory notification and a cohort study among university students

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ABSTRACT

Introduction: In 2012, an increase in mumps notifications occurred in Belgium, affecting young vaccinated adults. At the end of 2012, a mumps outbreak occurred at the Catholic University of Leuven KU Leuven in Flanders. We investigated the outbreak to estimate incidence, mumps vaccine effectiveness and to detect potential risk factors for the disease.
Methods: In June 2012, we set up mandatory notification in Flanders and we collected information on circulating genotypes from the National Reference Centre. We conducted a cohort study among KU Leuven students. We defined a case as self-reported parotitis, between September 2012 and March 2013. We distributed web-based questionnaires to a random sample of students. We calculated vaccine effectiveness by comparing the risks in students vaccinated twice with those vaccinated once. We estimated risk ratios (RR) to identify risk factors.
Results: From 16th June 2012 to 1st April 2013, 4061 mumps cases were notified to the regional public health office (30% were vaccinated once and 69% were vaccinated twice). All 16 samples collected at the KU Leuven were genotype G5. Of 717 participants of the cohort study, 38 (5%; 95%CI 4–8%) met the case-definition. All reported being vaccinated with at least one dose of mumps-containing vaccine. The incidence of mumps was 5% among those vaccinated twice and 16% among those vaccinated once (vaccine effectiveness of two doses compared to one: 68%, 95%CI −24% to 92%). The risk of mumps was lower among those vaccinated with two doses of mumps-containing vaccine ≤10 years before (RR: 0.33, 95%CI 0.10–1.02) and higher among students working in a bar (RR: 3.6, 95%CI 1.8–7.0).
Conclusions: Incomplete protection by two doses of mumps-containing vaccine, possible waning immunity and intense social contacts may have contributed to the occurrence of this outbreak in Flanders. Efforts to maintain high vaccination coverage with two doses remain essential. However, the reasons for low vaccine effectiveness must be further explored and additional immunological research for more immunogenic mumps vaccines is necessary.

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1. Introduction

Mumps, a viral infection, can cause mild to severe symptoms or be asymptomatic. The most characteristic feature of the disease is parotitis and swelling of the salivary glands. The risk of severe symptoms and complications increases in adults [1]. Sequelae include meningitis (1–10%), encephalitis (0–1%), oophoritis (5% of female cases), orchitis (15–30% of male cases), pancreatitis (4%) and deafness (0.005%) [1,2]. Mumps basic reproduction number ranges from 4 to 10, which is lower than measles [3]. Based on 2004 WHO data, 38% of the countries/areas world wide use mumps vaccine in their national immunization programmes. Among these, 63% use a one dose schedule and 37% use a two-dose vaccination schedule [4]. The introduction of mumps vaccine led to a decrease in reported rates. In countries using two doses (e.g., Norway, Denmark, Finland), rates decreased to <1/100,000 population. Seroconversion rates for one dose of the Jeryl Lynn strain mumps vaccine, used in the vaccination schedule in Flanders in Belgium, ranges from 80 to 100% [5]. Pre-licensure studies estimated that the efficacy of two doses Jeryl Lynn strain mumps vaccine reached 95%. However, during outbreaks, vaccine effectiveness for two doses ranged from 61% to 91% [6].

In 2002, the WHO European Region introduced a strategic plan to eliminate measles and prevent congenital rubella infection by 2010. The plan involved increasing vaccine coverage with the measles, mumps, rubella (MMR) vaccine to at least 95%. Hence, a parallel aim was to reduce annual reported rates for mumps to under 1/100,000 by country [4]. From 2006 to 2010, in Europe, mumps rates decreased from 8.7 to 1.98/100,000 [7]. However, at the same time, several countries reported large outbreaks [8–13]. From 2004 to 2005 on, one of the first large mumps outbreaks in a vaccinated population occurred in England and Wales [8], including 2,562 laboratory confirmed cases in 2012 [14]. From 2009, the Netherlands reported a mumps outbreak that started among students and evolved into a large national outbreak with 1662 cases until June 2013 [15]. These outbreaks and other outbreaks, such as those in the United States, shared common features [9]. First, young adults were most commonly affected. Second, cases clustered among students with intensive social contacts (e.g., classes, shared living facilities). Third, affected young adults were often vaccinated with two-doses of mumps vaccine.

In 1984, the general Flemish vaccination scheme included MMR vaccination with a first dose administered at the age of 10–12 months. In 1995, a second dose administered at the age of 10–12 years was added. The vaccination strain used in Flanders is Jeryl Lynn (MMRVax®, Priorix®) [16]. The vaccination coverage for children aged 18–24 months (first dose of MMR) and children aged 14 years (second dose of MMR) is estimated in Flanders using two-stage cluster sampling surveys, that take place every 4–5 years. The most recent coverage assessment was performed in 2012 [17].

In Belgium, incidence of mumps prior to general vaccination was estimated at 500/100,000 in 1985 and declined to 49/100,000 in 1994 [16]. Mumps is not a notifiable disease in Belgium. However, in Flanders, the regional public health office requires medical doctors and authorities of educational institutions to notify clusters of several diseases, including mumps. Between 1995 and 2010, smaller clusters of mumps cases and one outbreak in 1995/96 in partly vaccinated children aged 8–12 years were reported [6]. In the spring of 2011, regional public health authorities of Antwerp (a province of Flanders) reported a mumps outbreak with 164 cases, mostly among young adults [18]. In 2012, medical doctors from Ghent reported a new cluster of mumps among students of the University [19]. This outbreak spread to campuses and universities in other provinces. However, the absence of a comprehensive surveillance system prevented a full description of the disease burden and of the characteristics of mumps patients. On 16th of June 2012, after a risk assessment meeting ordered by the Flemish Ministry of Health, mandatory notification for mumps was introduced. The system of mandatory notification already existed for 35 infectious diseases and applied to every physician and clinical laboratory [20]. At the end of 2012, the medical service of the Catholic University of Leuven (KU Leuven), the largest university of Flanders (37,742 students), informed the regional public health service of a peak of mumps related consultations. We aimed to estimate the disease burden, describe the characteristics of cases, estimate vaccine effectiveness and identify risk factors for the disease.

2. Methods

In order to describe the situation of mumps in Flanders, Belgium, we present two related, but separate analyses , the epidemiology of mumps over all of Flanders by surveillance data collected through temporary mandatory notification, from June 2012 to April 2013 and a retrospective cohort study among one of the affected universities.

2.1. Surveillance data

2.1.1. Epidemiological methods

For the purpose of surveillance, a case was defined as a person who presented with uni- or bilateral swelling of the parotid or other salivary glands for more than two days without another apparent cause (possible case) and epidemiological link with another mumps case (probable case) and/or laboratory criteria by either detecting the mumps virus by PCR, mumps IgM antibodies or detecting a four-fold increase in mumps IgG antibodies (laboratory-confirmed case). Regional public health officers collected information on patient characteristics, symptoms, complications and self-reported vaccination status and stored it in a database common for Flanders. The mandatory notification of mumps was temporary and started on 16th of June 2012.

2.1.2. Laboratory investigations

Local health care providers collected oral fluid and serum samples and delivered them to the national Reference Centre (NRC). The reference centre received samples from all over Flanders. Analyses were done using an in-house developed real-time PCR targeting the SH protein from the mumps virus. Genotyping was also performed using an in-house developed test on saliva and nasopharyngeal secretions.

2.2. Retrospective cohort study

2.2.1. Study design and study population

We conducted a retrospective cohort study among students of the KU Leuven. We calculated the required sample size under the following assumptions; if we want to detect a difference as small as 5% in attack rate between those vaccinated and those unvaccinated and we are willing to assume that the attack rate in the vaccinated population is 15% at its highest, we would need a sample size between 227 and 1348. We assumed that the response rate would be around 50%. We therefore selected a simple random sample of 2000 students attending lectures between 24 September 2012 and 11 March 2013 (main cohort). We chose to select a second random sample from a specific population; students who worked in student bars at least twice a week (student bar-cohort). The bar managers from the 10 largest student bars were asked to distribute the survey.

2.2.2. Case definition

For the purpose of surveillance, we defined a case as any student at the KU Leuven with self-reported swelling and inflammation of

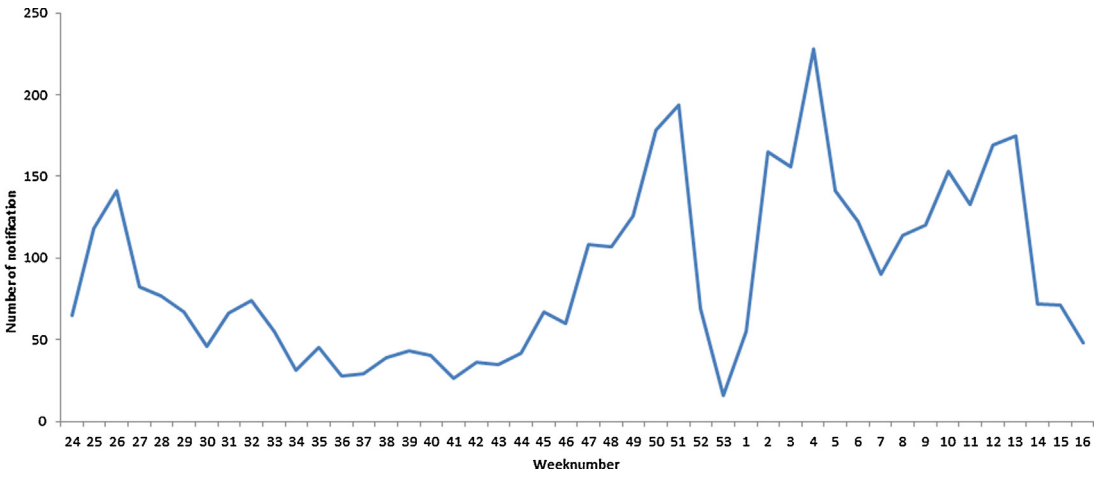

Fig. 1. Number of reported mumps cases by date of notification from 16/06/2012 until 16/04/2013, Flanders, Belgium.

the parotid glands between24th of September 2012 and 11th of March 2013.

2.2.3. Data collection

We collected information on personal characteristics (age, gender), mumps-related symptoms (using visual prompts), complications, possible previous mumps infections, contact with mumps cases, days absent from social activities, contact with health care providers and self-reported immunization status. We used a web-based questionnaire (Lime survey software, version 1.91). We sent invitations to the selected students on the 18th of March 2013, followed by a reminder one week later. We reviewed the medical files of the university medical service to obtain the documented immunization status of participants.

2.2.4. Data analysis

We described mumps cases by time, place and person. We calculated relative risks (RR) of mumps according to immunization status and a selection of risk factors along with 95% confidence intervals. We considered a p-value <0.05 as statistically significant. We extrapolated the incidence of self-reported parotitis to the complete student population of the KU Leuven. We calculated vaccine effectiveness (VE) as the difference in attack rate between those vaccinated twice and those vaccinated once over the attack rate in those vaccinated once. We calculated the time in years since the second vaccination based on the documented vaccination data.

We analyzed data using STATA 12.00 (STATA Corporation, College Station, TX, USA) and SAS 9.3 (SAS Institute Inc. 2011, TX, USA).

2.2.5. Human subject protection

Informed consent from all students who were included in the study was obtained. On December 14, 2012, the ethics committee of the hospital of KU Leuven approved the study protocol.

3. Results

3.1. Surveillance data

3.1.1. Epidemiology

Between June 16, 2012 and April 16, 2013, 4052 cases were reported from Flanders, of which 1187 were possible, 1294 were probable and 1540 were laboratory-confirmed (overall reported rates: 31.5/100,000 population). Reported cases of mumps peaked in December 2012 (Fig. 1). Most cases were reported in cities where universities are located, including Ghent (n = 510), Leuven (n = 419), Kortrijk (n = 415) and Antwerp (n = 365) (Fig. 2). Fifty-eight percent (n = 2364) of the cases were male and 58% (n = 2348) were between 15 and 25 years of age. Vaccination information was available for 1190 (29%) cases. Of these, 70% (n = 836) were vaccinated twice, 28% (n = 338) were vaccinated once and 2% (n = 16) were unvaccinated. Orchitis was reported in 11% (n = 145) of male cases for whom the status of complications was known. Other complications included meningitis (n = 8; 0.2%) and pancreatitis (n = 5; 0.1%).

3.1.2. Laboratory results

Between June 16, 2012 and April 16, 2013, 128 specimens were collected from Flanders and tested for mumps virus at the NRC. All specimens were tested by PCR; 53% were confirmed. Genotyping was performed in41 specimens. All, including the15 specimens received from the medical service of the KU Leuven, were genotyped as G5 (subtype Groningen 2010).

3.2. Retrospective cohort study

3.2.1. Description of the outbreak

Of the 2000 students approached, 717 completed the web-based questionnaire (response = 36%);47 of the students frequently

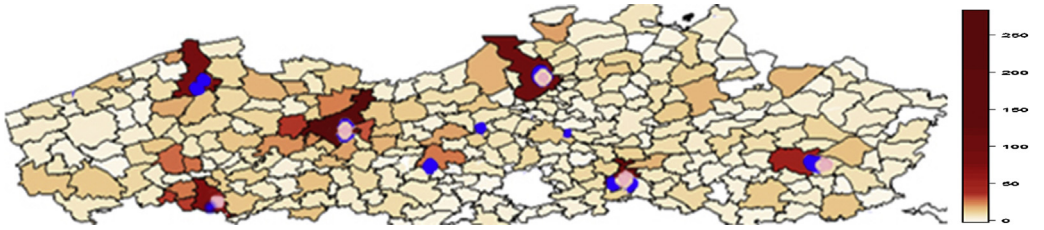

Fig. 2. Reported cases of mumps per municipality, mandatory notification data 16/06/2012 until 16/04/2013. Pink dot depicts the location of the universities and blue dots the location of colleges, Flanders, Belgium, 2012/2013 (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.).

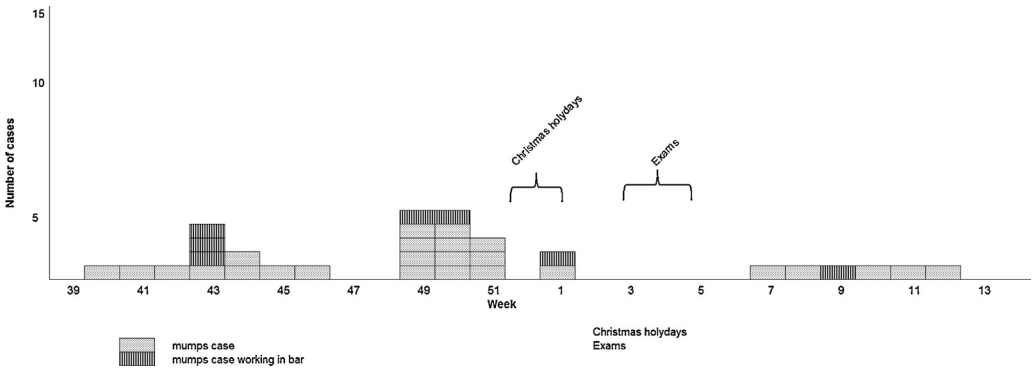

Fig. 3. Mumps cases by week of onset, Catholic University of Leuven, Leuven, 24/09/2012–11/03/2013.

working in student bars responded. Sixty-five percent (n = 496) of the respondents were female and the median age was 22 years (range 17–59).

Of the 717 respondents in the main cohort, 38 students reported parotitis (5.0%, CI 4.4–7.8%), suggesting that 2000 (95%CI 1662–2378) parotitis cases may have occurred among all 37,742 KU Leuven students in a period of seven months.

Eighty-two percent (n = 31) and 71% (n = 27) of the cases reported pain while swallowing and earache, respectively. Other symptoms frequently reported by the cases included headache (n = 26; 68%), fever (n = 22; 58%) and fatigue (n = 20; 53%). Two (8%) of the male cases reported orchitis and two (4%) cases reported meningitis; 34 (72%) cases visited a physician and one case was hospitalized.

Mumps cases started to occur from October 2012, peaked at the end of December, decreased during the Christmas holidays and exams and re-increased in February 2013 as classes resumed (Fig 3).

The median age of cases was 21.5 years (range 18–26) and 53% (n = 25) were male. No significant differences were found between the main cohort and the student bar-cohort. The gender-specific attack rate was 4% for females and 9% for males (RR: 2.1, 95%CI 1.2–3.7). The duration of mumps symptoms ranged from 1 to 20 days (median: 6.5 days) while absences from classes ranged from 1 to 20 days (median: 4.4 days).

The risk of mumps was higher among students working in student bars (9/47, 19%) than among others (38/717, 5%, RR: 3.6, 95%CI 1.9–7.0). Even after adjustment for documented immunization status the RR differed significantly from one (adjusted RR: 3.4; 95%CI 1.1–11).

3.2.2. *Vaccination status and vaccine effectiveness*

Of all study participants, 95% (n = 729) reported their vaccination status. Of those, 3% (n = 30) reported that they had not been vaccinated, 37% (n = 290) reported being vaccinated once and 54% (n = 412) reported being vaccinated twice (Table 1). For 33% (n = 259) of the respondents, documented vaccination status was available in the medical files of the KU Leuven. Among those with a documented vaccination status, none were unvaccinated, 5% (n = 12) were vaccinated once and 95% (n = 247) twice. The risk of mumps among students who were vaccinated twice (attack rate 5%) was lower than among those who were vaccinated once (attack rate 17%). The two dose vaccine effectiveness, as compared to a single dose, was estimated at 68% (RR: 0.32, 95%CI −24% to 92%).

The risk of mumps among those vaccinated with two doses within the last 10 years (attack rate 3%) was lower than among those vaccinated with two doses ≥11 years earlier (attack rate 9%). The difference was not significant (95%CI 0.10–1.02).

4. Discussion

Between June 2012 and April 2013, the Flemish region of Belgium reported an increased number of mumps cases, mostly among young vaccinated adults and in cities with universities. At the end of 2012, a mumps outbreak occurred among highly vaccinated students in the largest university of Flanders. The estimated vaccine effectiveness for mumps for two doses compared to one was 68% (95%CI −24% to 92%), with indications of waning immunity over time.

We estimated an attack rate of mumps of 5% during this outbreak. This finding was consistent with results of several other European studies in similar settings, where the reported attack rates of mumps ranged from 1% to 7% among vaccinated populations [10,21]. However, in the Netherlands, during an outbreak among university students, the attack rate was higher (13%) [11].

Mandatory notification and cohort study data suggested that the incidence was higher among males. This may have an immunological explanation. In vitro studies indicated that females have a

Table 1
Risk of mumps by vaccination status, KU Leuven, Flanders, Belgium, 2012–2013.

Exposures categories	Number of doses	Number of cases	Total	%	Relative risk	95% Confidence interval	Vaccine effectiveness %	95% Confidence interval
Self-reported vaccination	0	0	30	0	N/A	N/A	N/A[a]	N/A
	1	24	290	8	Reference	Reference	Reference	Reference
	2	21	412	5	0.61	0.34–1.07	39	−7.4 to 66
Documented vaccination	0	0	0	0	N/A	N/A	N/A	N/A
	1	2	12	17	Reference	Reference	Reference	Reference
	2	13	247	5	0.32	0.08–1.24	68	−24 to 92
Time since second dose (years)	0–10	4	132	3	0.33	0.10–1.02	67	0–89
	≥11	11	122	9	Reference	Reference	Reference	Reference

[a] Non applicable.

greater immune response to vaccination than males [22]. Moreover, seroprevalence studies conducted in the Netherlands and Belgium reported lower levels of mumps-induced antibodies in males [23,24].

The documented vaccination coverage for two-doses of mumps-containing vaccine among our study participants was 95%. Seroprevalence studies suggest that a two-dose coverage of ≥95%for mumps protects populations from outbreaks [25,26]. In 2012, a vaccination coverage survey in the Flemish region reported 92.5% coverage for the second dose of MMR [17]. A coverage survey, conducted in 2005, among the birth cohort that was highly affected during the 2013 outbreak (birth year: 1991) estimated a vaccination coverage of 84% for the second dose [27]. Therefore, the vaccination coverage in Flanders may have been insufficient to protect the population against outbreaks. The low proportion of participants for whom medical files were available at the university medical service may have biased our vaccination coverage.

In our study, we could not obtain a significant vaccine effectiveness estimate. We obtained a vaccine effectiveness estimate of 68% for the second dose as compared to only one dose, indicating the benefit of vaccinating twice, but also indicating that a two dose vaccination offers incomplete protection. Results of a 2012 Cochrane review indicated a two-dose vaccine effectiveness of 83–88% for lab-confirmed cases [28]. In outbreak situations, case definitions and determination of vaccination status may influence the vaccine effectiveness estimates.

Differences between the wild type virus and the vaccine strain may also explain the low vaccine effectiveness estimate in our study. Low antibody avidity to wild-type virus, as the mismatch between the vaccine genotype and that of the circulating mumps virus strains may facilitate immune escape [29]. In our study, all isolates were genotyped as G5, suggesting that this was the circulating wild type virus. Reports indicated that cross-protection between the vaccine genotype A and the circulating wild strains (mainly C, D and G) is incomplete. However, other studies have documented that clinical isolates were successfully neutralized by vaccine induced immunity and a higher avidity of mumps antibodies was observed amongst vaccinated cases [30].

Waning immunity could also explain our effectiveness estimate. Those who were vaccinated more than 10 years earlier were at greater risk of developing mumps than those vaccinated later, this simple analysis is however limited, since no correction for possible confounding factors is done. Other studies report diverse results on waning immunity. A 2003 Belgian study and a 2006 study in the USA, both in outbreak settings, reported that protection against mumps declined with increasing time since last vaccination [6,31,32].

A specific second sample of students frequently working in bars was compared to the first random sample of students. The main purpose of this design was to evaluate if dense social contacts would affect attack rates. We felt that the response rate on our survey would suffers from questions such as time spent in student bars and also that the quality of answers on such questions might be low. We therefore selected a second cohort. This second cohort worked in student bars for 2–3 evenings a week. This was used as a proxy for dense social contacts. Differentiating student bar workers from the other students in the first sample would have also been possible, but would have required a much larger first sample, since only a small proportion of students worked in bars. No students were present in both cohorts. It is possible that confounders were present as the second cohort might differ from the general student population on more than working in bars often crowded with a lot of peers. Age, gender and vaccination coverage were however comparable between cohorts. We found a higher attack rate in students working in student bars as compared to the general student population. Other studies in populations with a high coverage of two doses of mumps-containing vaccine have also reported close and prolonged social contacts as an important risk factor for transmission [9]. Intense social contacts in close environments may contribute to over come vaccine-induced protection. Avoiding these whilst infectious will limit the spread of a mumps outbreak. An important limitation of such a control measure is however that persons might be infectious up to 6 days before exhibiting symptoms [33]. The specific contribution of social activities in overcoming vaccine induced protection, certainly if this protection is incomplete due to vaccine effectiveness, incomplete coverage and waning, is a topic for further research.

Our study is subject to certain limitations. First, our use of self-reported clinical symptoms de facto consisted in parotitis surveillance. Mumps can be asymptomatic, without parotitis, and on the other hand parotitis can be caused by other pathogens, especially when incidence of other respiratory infections is high. This may have underestimated or overestimated the incidence of mumps. The clinical definition of mumps as uni- or bilateral swelling of the parotis or any other salivary gland for a minimum of two days without a known cause is however highly specific for mumps in outbreak settings. Using only laboratory confirmed cases also had limitation since laboratory confirmation is challenging in highly vaccinated populations [34]. Second, the low response rate (36%) may have introduced selection bias. E.g. those who suffered might be more willing to answer the questioner than others.

Third, availability of documented vaccination data was limited. The low proportion of participants for whom medical files were available at the university has resulted in large confidence intervals for vaccine effectiveness. Based on the documented vaccination status we were not able to compare fully vaccinated students to unvaccinated students, since no students were documented as unvaccinated. These small numbers are a limitation and do not allow us to sufficiently quantify vaccine effectiveness. The availability of vaccination records will change in the near future, as almost all relevant data will be stored in the newly created immunization database “Vaccinnet” for Flanders [35].

5. Conclusions and recommendations

A large mumps outbreak affected vaccinated young adults in Flanders. Incomplete protection by the mumps component of the MMR vaccine, possible waning immunity over time and the intense social contacts may have contributed to the occurrence of a mumps outbreak in the highly vaccinated student population in Flanders.

As the risk for mumps was higher in students working in bars, we conclude that social activities play an important role in the transmission of mumps. The advice to avoid social activities whilst infectious should be given to all possible cases. The main preventive measure remains vaccination and efforts towards a high vaccination coverage (>95%) remain essential. The reasons for outbreaks in highly vaccinated populations must however be further explored and additional immunological research towards more immunogenic mumps vaccines is necessary.

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